

T H O R A T E C®
C O R P O R A T I O N

INTRODUCTION AND OPENING REMARKS

Donald A. Middlebrook
Vice President, Regulatory Affairs and Quality
Assurance
Thoratec Corporation

PRESENTATION OUTLINE

- Introduction and Opening Remarks
- Device Overview
- Clinical Results from REMATCH Trial
- Summary and Closing Remarks

INTRODUCTION AND OPENING REMARKS

Presenters:

Victor Poirier	Chief Technology Advisor	Thoratec Corporation
Dr. Eric Rose	REMATCH PI & Chairman, Dept. of Surgery	Columbia-Presbyterian Medical Center, NY
Dr. Lynne Warner Stevenson	Medical Management Committee Chair, Director, Cardiomyopathy and Heart Failure	Brigham & Woman's Hospital, Boston

INTRODUCTION AND OPENING REMARKS

Thoratec Corporation Overview:

- Company Founded in 1976
- Merged with Thermo Cardiosystems in February 2001
- Product Focus
 - Circulatory Support
 - Vascular Grafts
 - Diagnostic Blood Testing
- Corporate Offices – Pleasanton, California
- 700 Employees Worldwide
- World Leader in Cardiac Assist Devices

INTRODUCTION AND OPENING REMARKS

Thoratec HeartMate VE LVAS; PMA P920014/S16

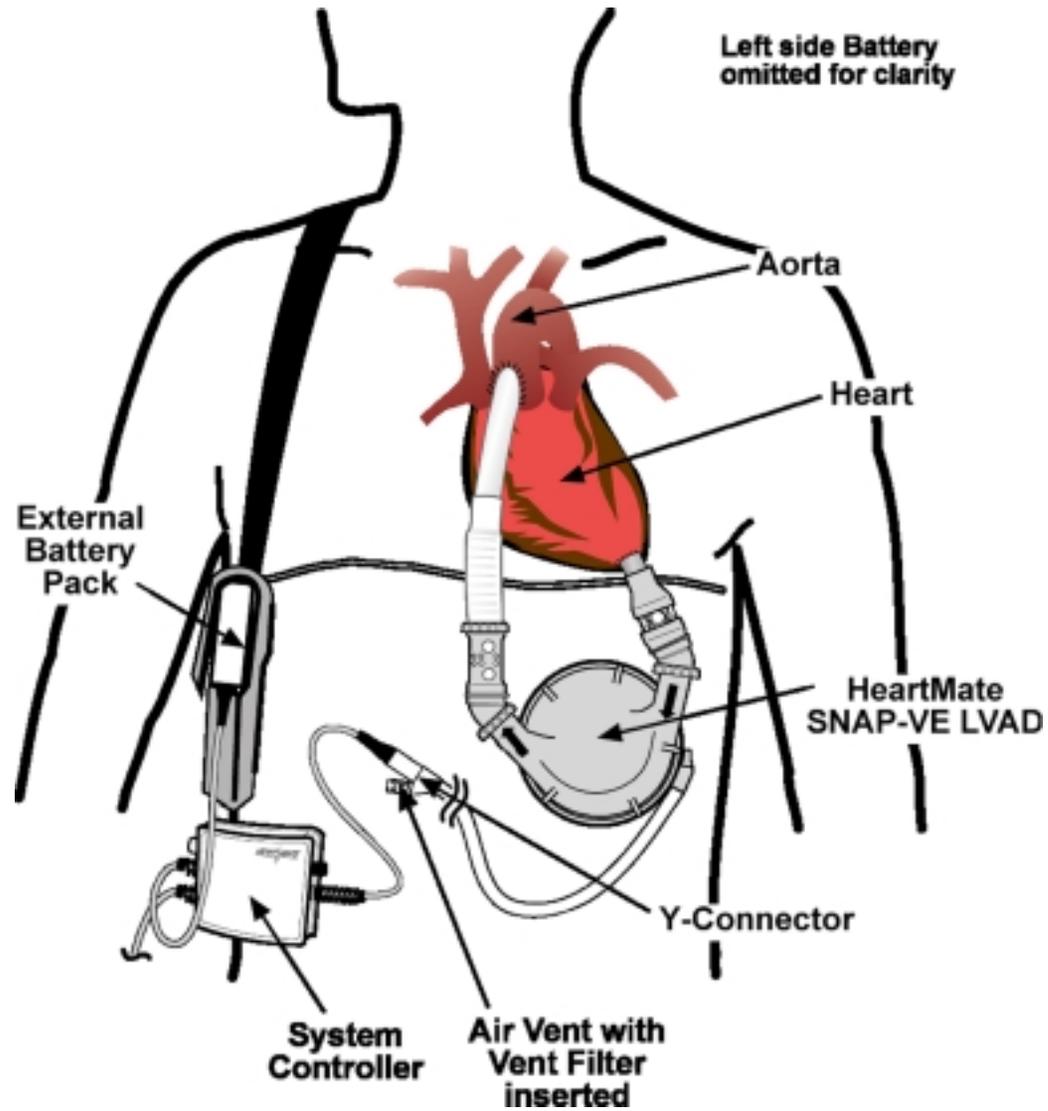
- Contains Results from REMATCH* Trial
- Landmark RCT: HeartMate VE LVAS vs. Optimal Medical Management
- Cooperative Agreement between Thoratec, NIH/NHLBI and Columbia University
- PMA seeks FDA Approval to Expand Current HeartMate VE LVAS Indications For Use to Include:
 - Patients with end-stage left ventricular failure who are ineligible for cardiac transplantation

* *R*andomized *E*valuation of *M*echanical *A*ssistance in the *T*reatment of *C*ongestive *H*eart failure

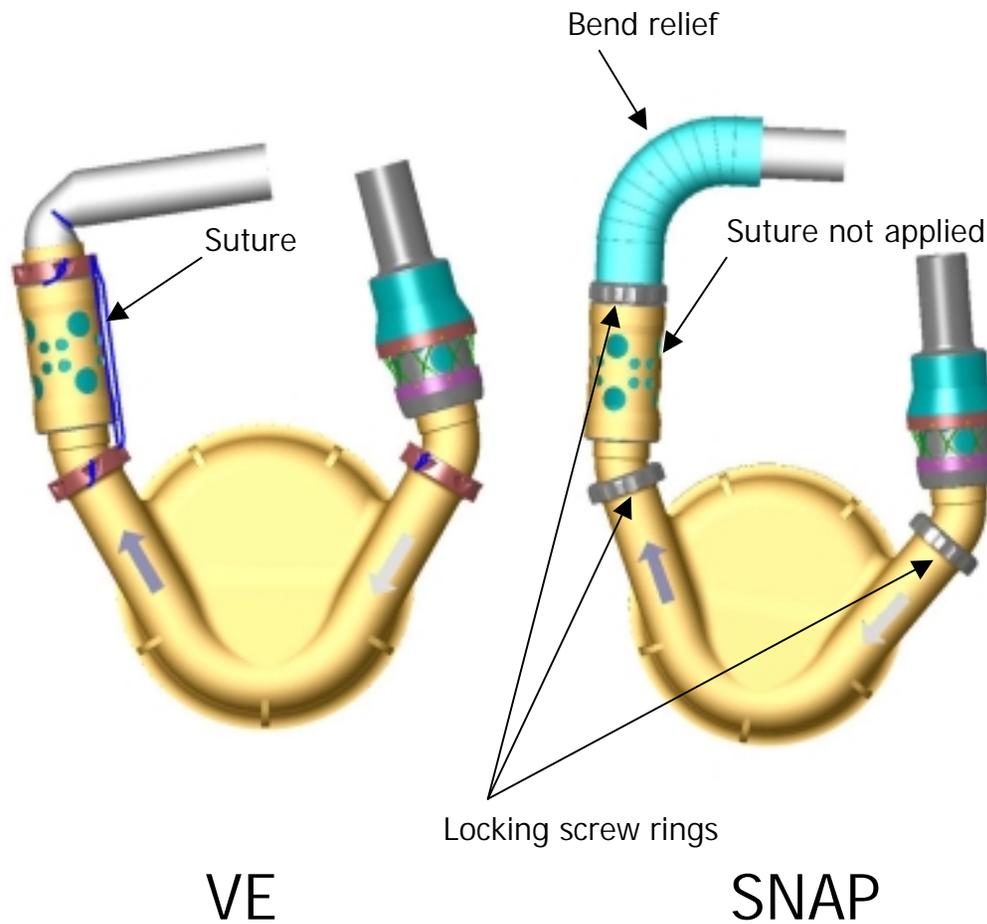
DEVICE OVERVIEW

Victor Poirier
Chief Technology Advisor
Thoratec Corporation

DEVICE OVERVIEW



VE vs SNAP Changes



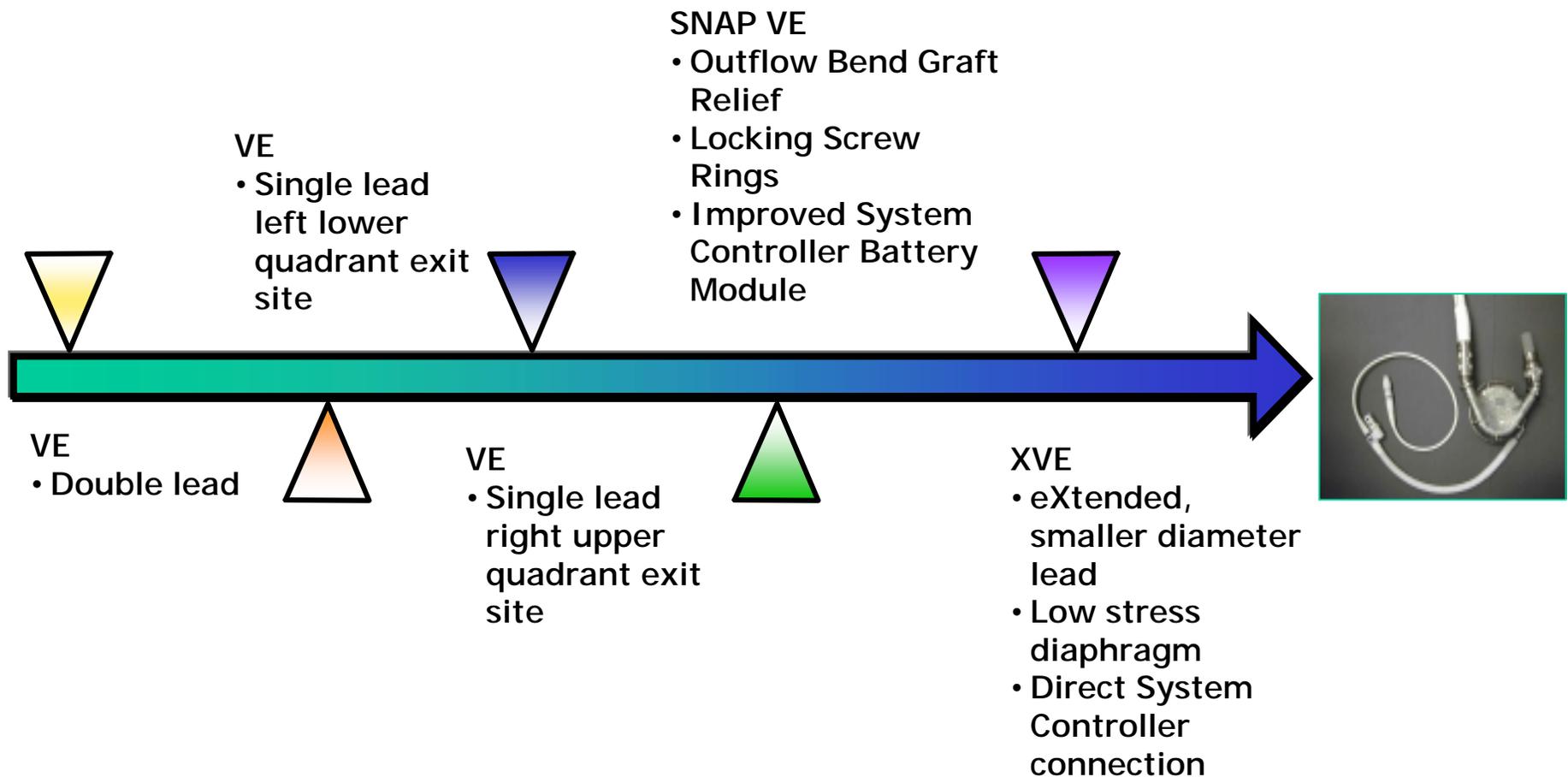
VE LVAD Reliability

Long term *in-vitro* testing:

- 88% chance that LVAD free of critical failures at 1 year
- 76% chance that LVAD free of critical failures at 2 years
- 3.1 year estimated mean time to failure

All based on 90% confidence intervals

HeartMate[®] VE LVAS Continuous Improvement



Evolution of the HeartMate LVAS

Average duration / maximum duration of support

REMATCH Trial (1998-2001)

344 days* / 1130 days*

PREMATCH Trial (1996-1998)

276 days / 607 days

HeartMate VE Bridge to Transplant Trial (1991-1998)

113 days / 691 days

HeartMate IP Bridge to Transplant Trial (1986-1994)

69 days / 344 days

Model 7/10 LVAD Trial (1975-1988)

4 days / 41 days

*Ongoing patients

Conclusions

- VE LVAS is a clinically proven technology for bridge to transplant
- Worldwide VE LVAS experience provides strong platform for expanded indication
- Company dedicated to circulatory support and heart failure patients
- Commitment to continuous improvement

REMATCH TRIAL CLINICAL RESULTS

Eric Rose, MD
REMATCH Principal Investigator
Chairman, Department of Surgery
Columbia University
New York, NY

Summary of Critical Clinical Findings

Efficacy:

- Survival benefit is clear and clinically meaningful and QOL is equivalent to, if not better than, OMM.

Safety:

- Incidence of adverse events in context of mortality reduction and QOL trends provides reasonable assurance of safety.

Conclusion:

- The VE LVAS is a scientifically validated alternative therapy for end stage heart failure patients who are not candidates for cardiac transplantation.

Clinical Results from REMATCH Trial

Discussion Outline:

- History of the REMATCH Trial
- Trial Design and Administration
- Summary of Patient Population
- Effectiveness Results
- Safety Results
- Summary

History of the REMATCH Trial

- Need for treatment options in end stage heart failure patients
- Positive experience with VE LVAD
- Pilot Trial (1996 – 1998): 10 controls, 11 LVADs
 - Randomization shown to be feasible
 - Clinical equipoise supported, thus randomization remained ethical
- REMATCH Trial enrollment commenced May 1998

Design of REMATCH Trial

- Cooperative agreement between Thoratec, Columbia University and NIH/NHLBI
- Independent Coordinating Center (InCHOIR)*
- Multicenter, randomized controlled trial
- Patients & physicians not blinded to treatment assignment
- Prospective plan for interim analyses
- Intent to treat analysis
- Primary statistical analysis: Kaplan – Meier and Logrank

* *I*nternational *C*enter for *H*ealth *O*utcomes and *I*nnovation
*R*esearch

To Control Bias

- Randomization
- Independent Coordinating Center (InCHOIR)
- Thoratec blinded to control data
- Investigators, InCHOIR blinded to overall data
- Credentialed investigators: cardiologist and surgeon
- Gatekeeper: reviews each patient eligibility
- Independent Data Safety & Monitoring Board and Morbidity & Mortality committee
- Medical and Surgical Management committees

Key Study Objectives

- **Efficacy:** To evaluate the effect of VE LVAS on the survival of patients with end stage chronic heart failure who are ineligible for cardiac transplantation
- **Safety:** Document and analyze adverse events and the incidence of device malfunction and failure

Secondary Study Endpoints

- Quality of Life
- Functional status
- Days in and out of hospital
- Cardiovascular mortality
- Cost

Key Study Assumptions

- Patients and clinicians would not adopt LVAD unless all-cause mortality over 2 years reduced by 1/3 or more
- Safety performance of device documented through bridge to transplant experience
- QOL with LVAD should equal or exceed OMM group

Sample Size and Power

Power:

- Study powered for survival and not secondary objectives
- Survival over time is roughly exponential and that the hazard ratio (LVAS to OMM) is 0.56

Sample Size/Endpoint:

- Endpoint is number of deaths, not pts enrolled
- 92 deaths required to have 80% power in a logrank test
- Study designed to allow up to 140 pts

Randomization

- Patients randomized between LVAD and OMM arm in a 1:1 ratio
- Stratified by study center
- Blocked to maintain balance in center over time
- Block sizes randomly selected to prevent manipulation of treatment assignment

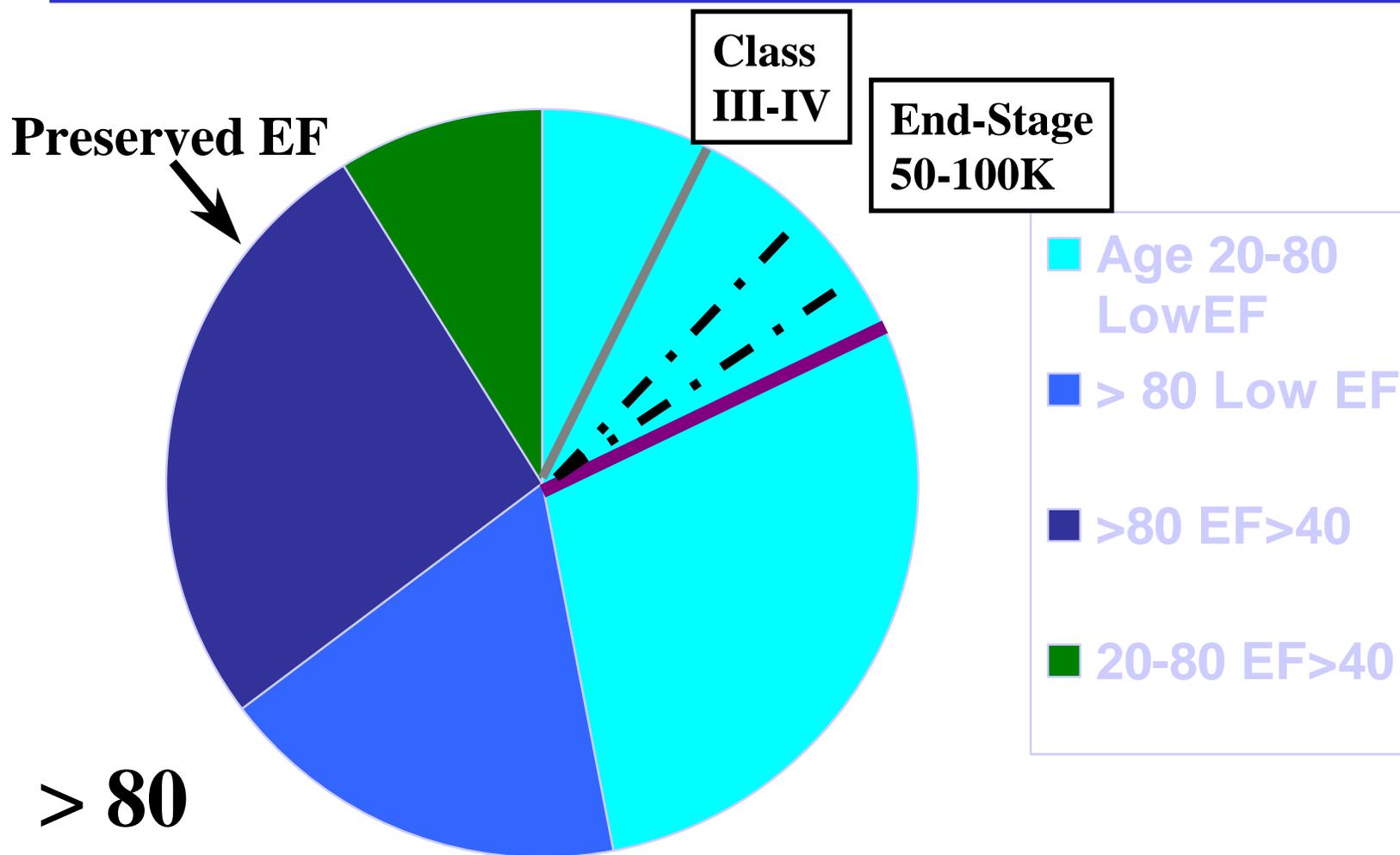
REMATCH Study Sites

- Columbia Presbyterian Med Ctr
- Cleveland Clinic Foundation
- Texas Heart Institute
- St Lukes Med Ctr, Milwaukee
- Temple University Hospital
- Rush Presbyterian Med Ctr
- Inova Fairfax Hospital
- LDS Hospital
- Ochsner Clinic
- Sharp Memorial Hospital
- Univ of Iowa Hospital & Clinic
- Univ of Michigan Hospital
- Univ of Minnesota Med School
- Brigham & Women's Hospital
- Nebraska Heart Institute
- Loyola University Med Ctr
- West Penn Allegheny Health Systems
- Univ Washington Med Ctr
- Univ Alabama
- Univ of Texas Southwest Med Ctr
- Jewish Hospital, Louisville

REMATCH TRIAL CLINICAL RESULTS

Lynne Warner Stevenson, MD
Chair, Medical Management Committee
Director, Cardiomyopathy & Heart Failure
Brigham & Women's Hospital
Boston, MA

Heart Failure Populations



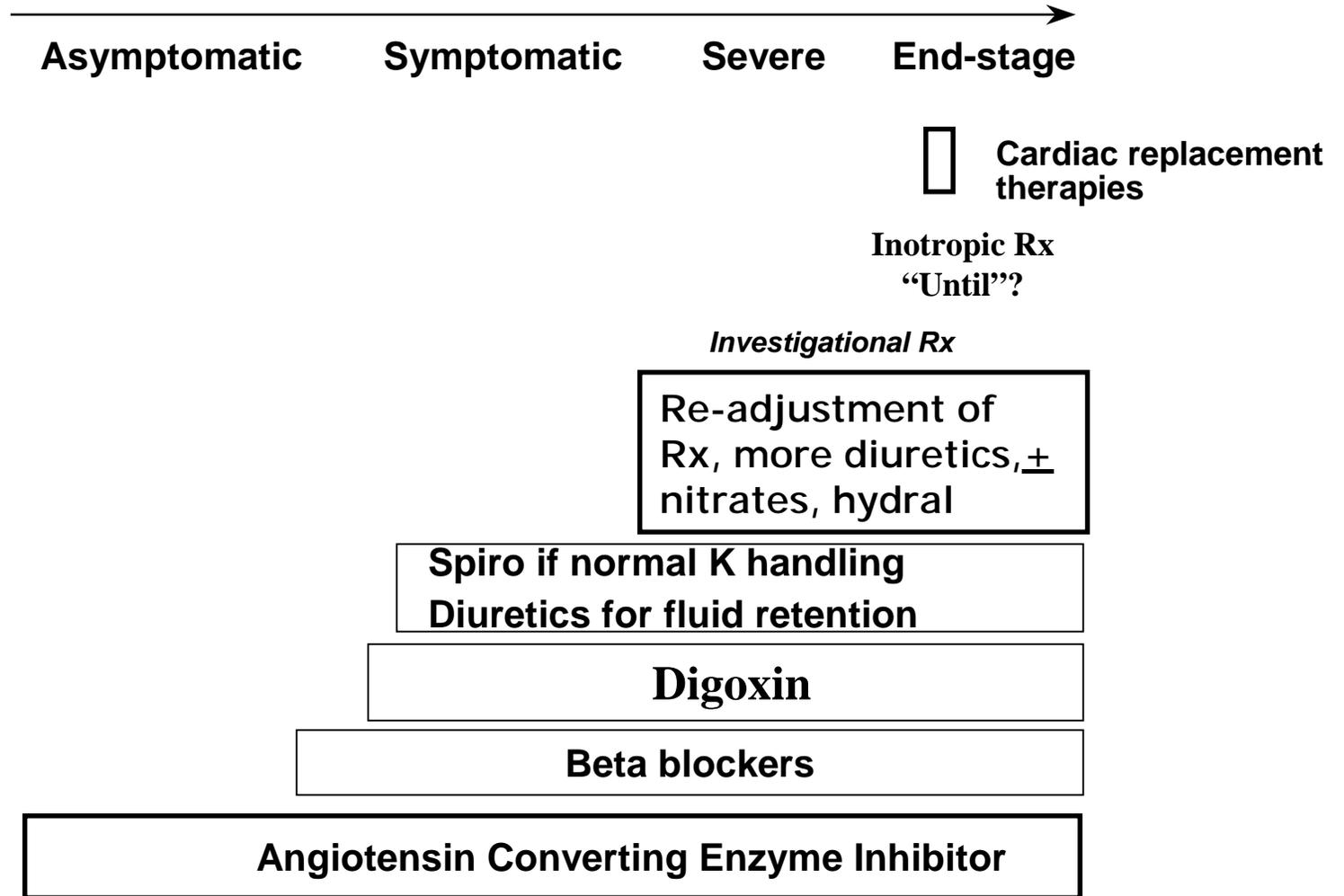
REMATCH Eligibility Criteria

- NYHA Class IV symptoms for 60 out of 90 days on ACEI, digoxin, diuretics
- LVEF \leq 25%
- Peak $VO_2 \leq$ 14 ml/kg/min or IV inotrope dependent
- Ineligible for cardiac transplantation

Reasons patients not transplant candidates

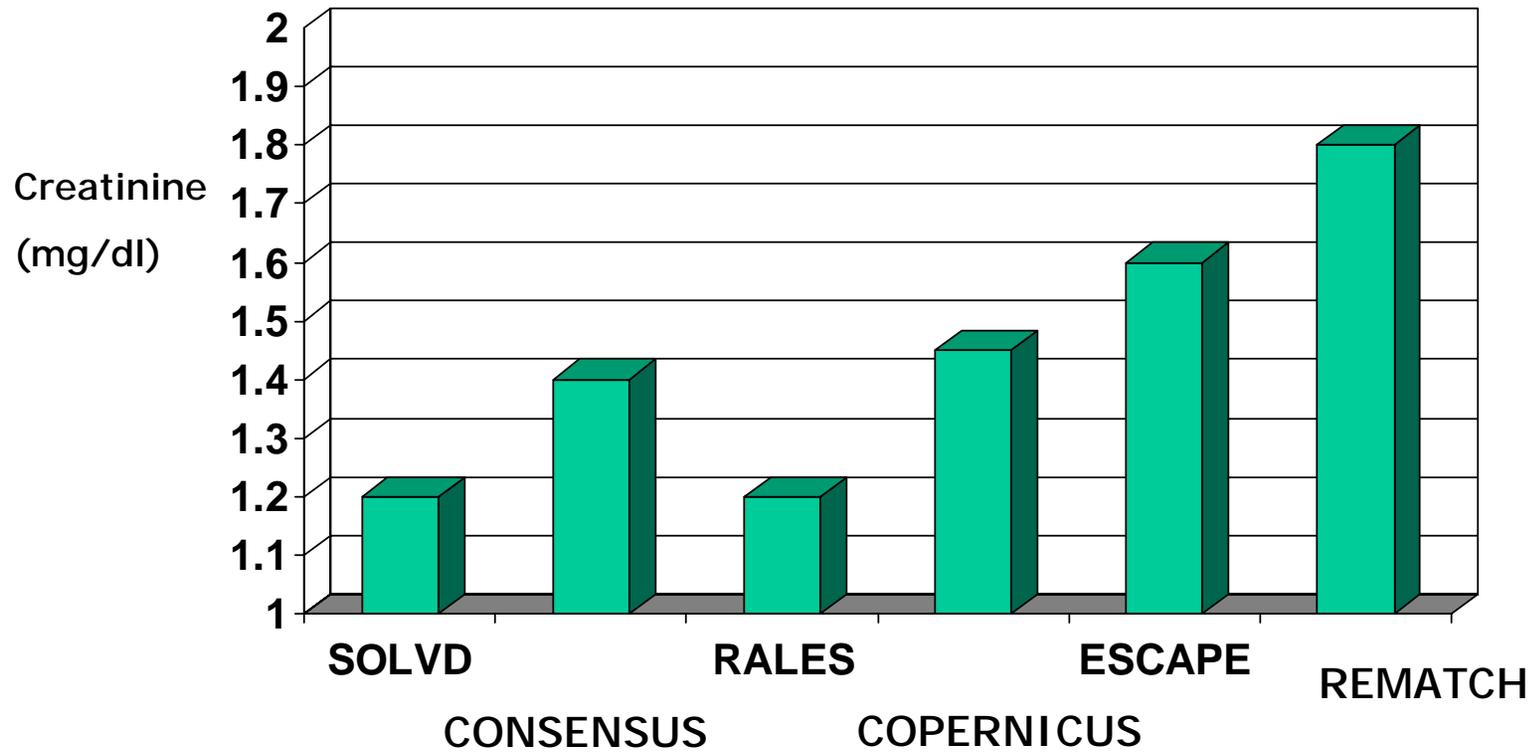
- Age \geq 65 years
- Insulin dependent Diabetes Mellitus with end-organ damage
- Chronic renal failure
- Significant irreversible comorbidity
 - Cancer
 - Obesity
 - Pulmonary hypertension

Escalating Therapy for Heart Failure



HEART FAILURE MANAGEMENT PROGRAMS HOSPICE

Renal Dysfunction in Heart Failure Trials

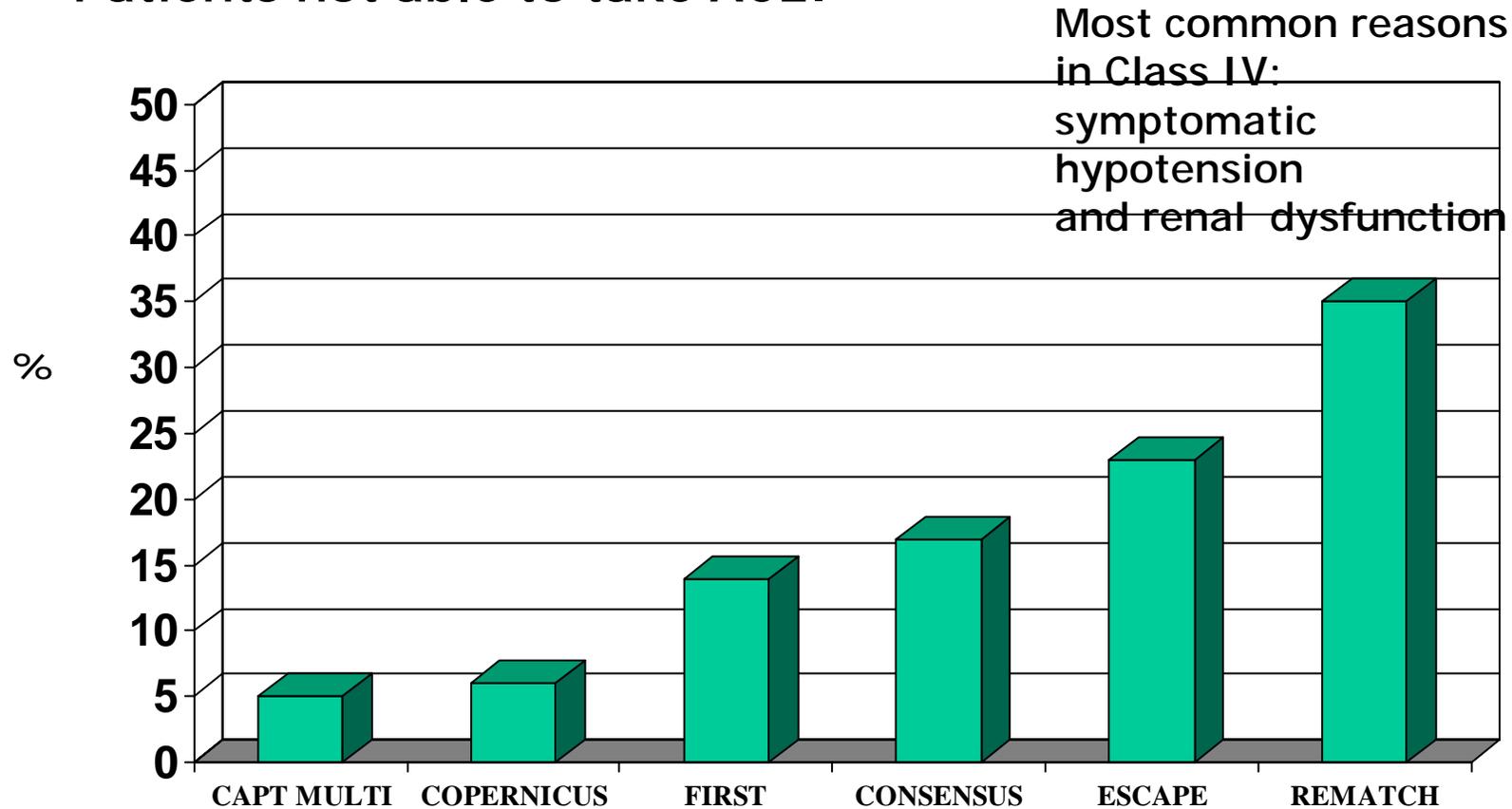


REMATCH Therapies at Baseline

Medication	% of OMM Patients (N = 61)
ACE Inhibitors	53%
Beta Blockers	20%
IV Inotropes	75%
Diuretics	97%
Digoxin	85%
Amiodarone	46%

ACEI Intolerance in Advancing Heart Failure

Patients not able to take ACEI



Hospitalized Patient Populations After ACEI Rx

	CONS	VMAC	OPT	Profile B-Warm	FIRST ^T	Profile C-cold	REMATCH OMM
SBP	119	121	120	114	107	103	103
LVEF		26%	24%	26%	19%	21%	17%
Na	138		138	137	138	136	135
6 mo Mortality	29%	23%	10% 2 mo	20%	37%	34%	48%

Medical Management of OMM Population

Medications	Baseline	Month 1	Last
Inotropes	75%	63%	70%
1	51	50	57
≥ 2	25	13	14
Diuretics	97	98	93
Aldosterone	39	39	30
Other	26	33	30
ACE Inhibitors	53	65	45
Hydralazine	16	22	18
Nitrates	43	39	41
Beta Blockers	20	13	11

Profiles of Heart Failure

(Including ACEI as tolerated, diuretics, digoxin)

	REMATCH	FIRST	PROMISE	COPERNICUS	SOLVD
LVEF (%)	17	19	21	20	28
NYHA	IV	IV	III-IV	IIIB-IV	II-III
SBP	103	105	115	123	120
Na	135	137	139	137	140
6 mo mortality	45%	37%	28%	10%	9%
1 year mortality	76%	49%	40%	18.5%	16%

REMATCH: Use of IV Inotropic Agents

OMM Manual:

“Every attempt should be made to discontinue IV inotropic agents prior to discharge from the hospital. This will often require careful titration of vasodilating regimens and volume status as the inotropic therapy is weaned. Some patients will have symptomatic hypotension on an ACEI dose that was tolerated during dobutamine infusion and should not be considered to have failed weaning until lower ACEI dose, and if necessary, substitution of another vasodilator regimen has been attempted. ...” June 1999

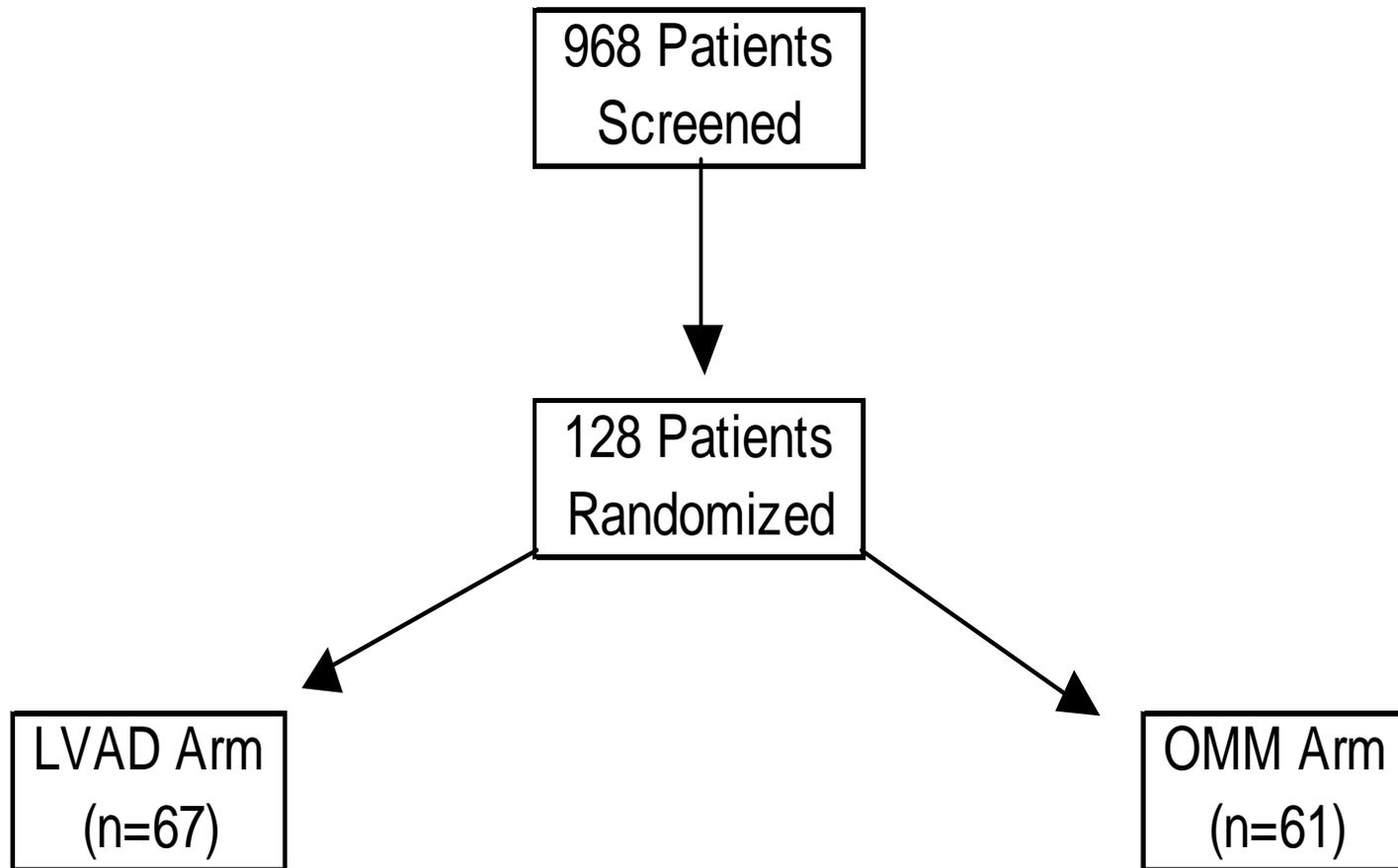
Summary of Patient Population

- REMATCH patients are a sicker patient population
- Patients assigned to medical management arm were optimized

REMATCH TRIAL CLINICAL RESULTS

Eric Rose, MD
REMATCH Principal Investigator
Chairman, Department of Surgery
Columbia University
New York, NY

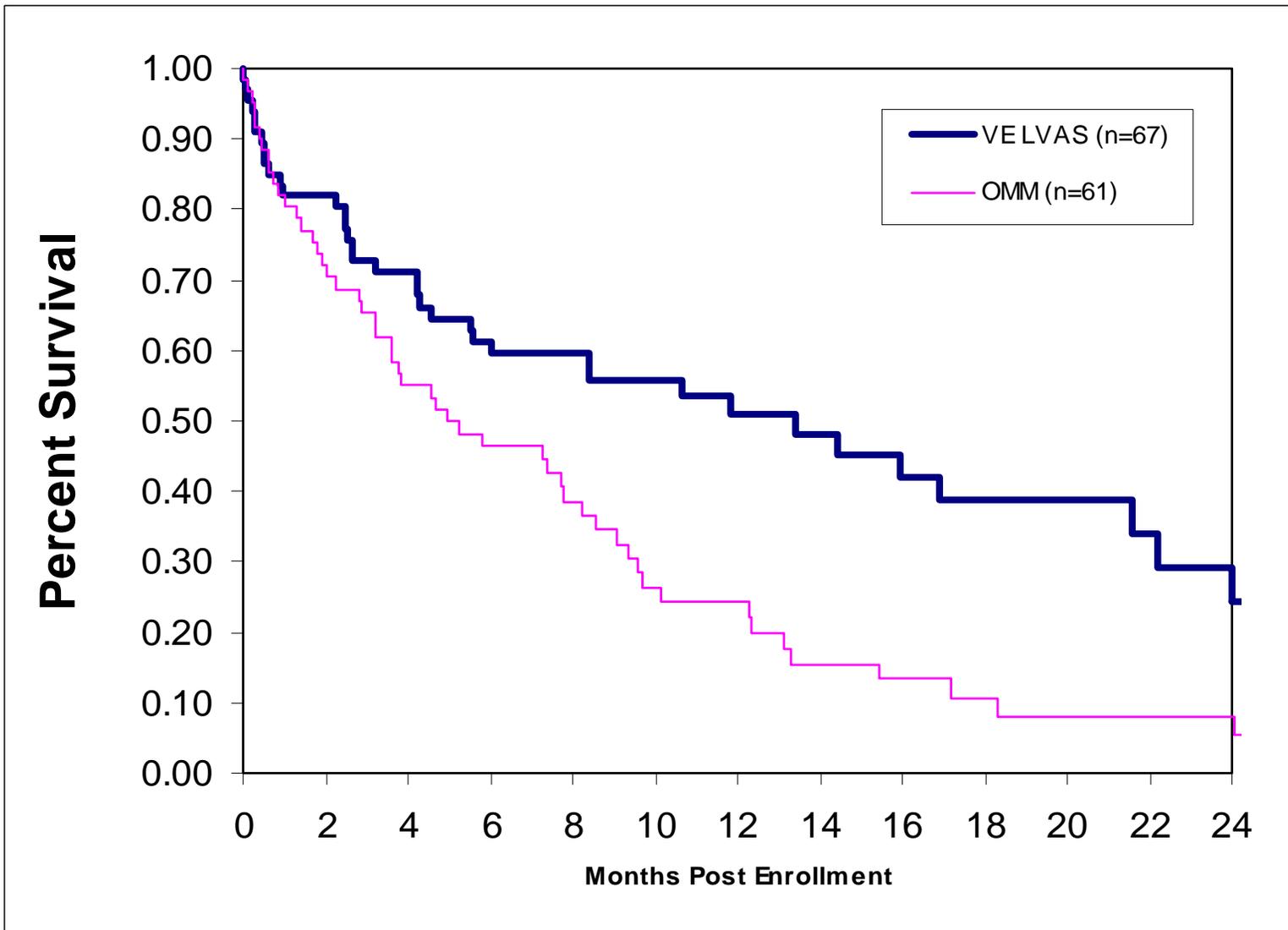
Patient Enrollment



Baseline Characteristics

Baseline Characteristic	LVAD (N=67)	OMM (N=61)	P
Age (years)	66±9.1	68±8.2	0.22
LVEF (%)	17±5.3	17±4.5	0.86
Cardiac Index (l/min/sq.m)	1.9±0.5	2.0±0.6	0.19
Serum Creatinine (mg/dl)	1.8±0.7	1.8±0.7	0.48
IV Inotropes (%)	64	75	0.18
MLHF (Total score)	76±17	75±17	0.76

Kaplan-Meier plot illustrating the probability of survival of LVAS versus OMM patients after 92 deaths. Logrank analysis: $P=0.003$



Effectiveness Results

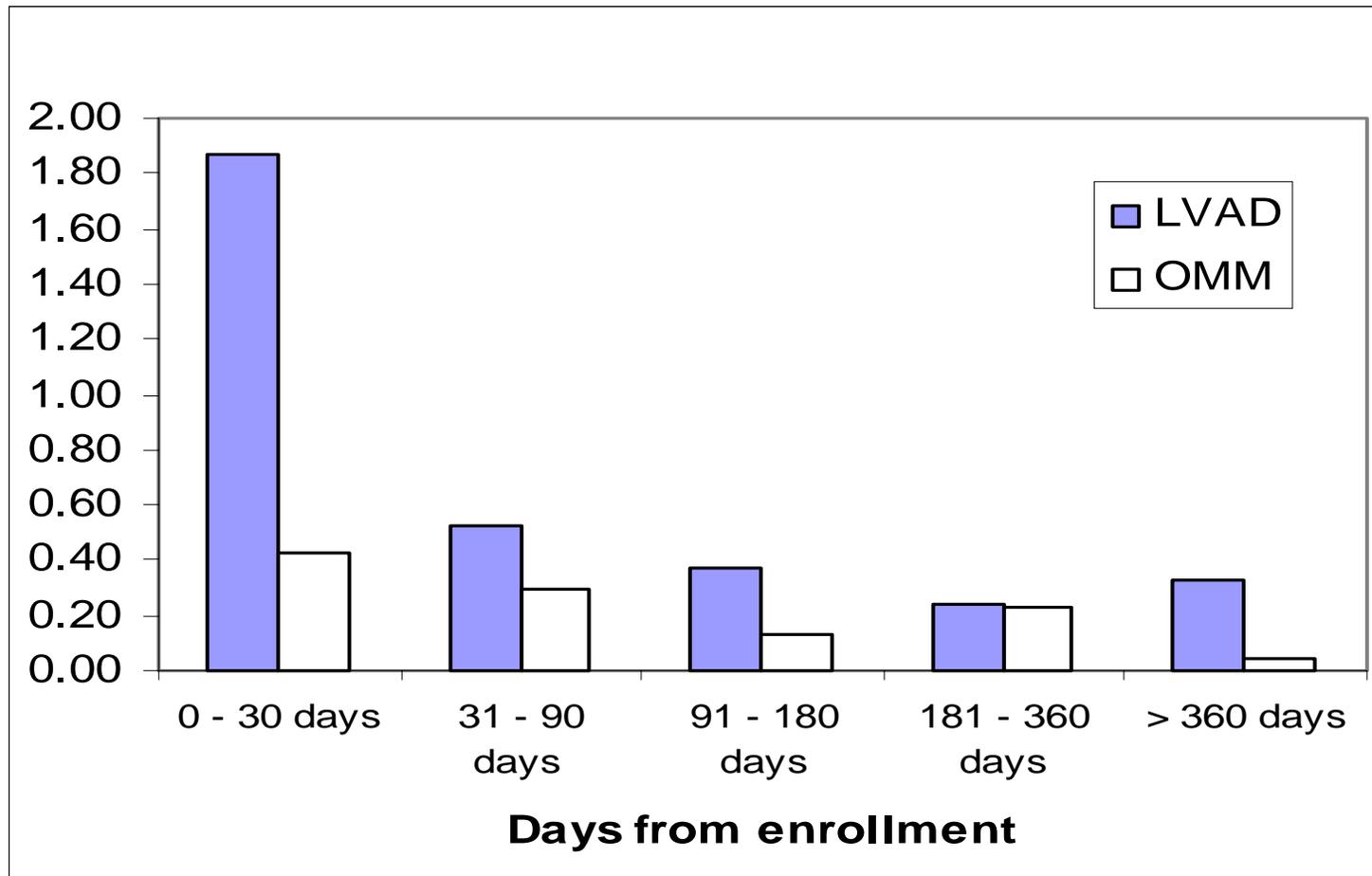
- 1 year survival doubled
- Absolute reduction of mortality rate of 27% at 1 year
- 2 year survival tripled
- Median Survival Time 408 days for LVAS patients vs 150 days for OMM

Effectiveness Conclusion

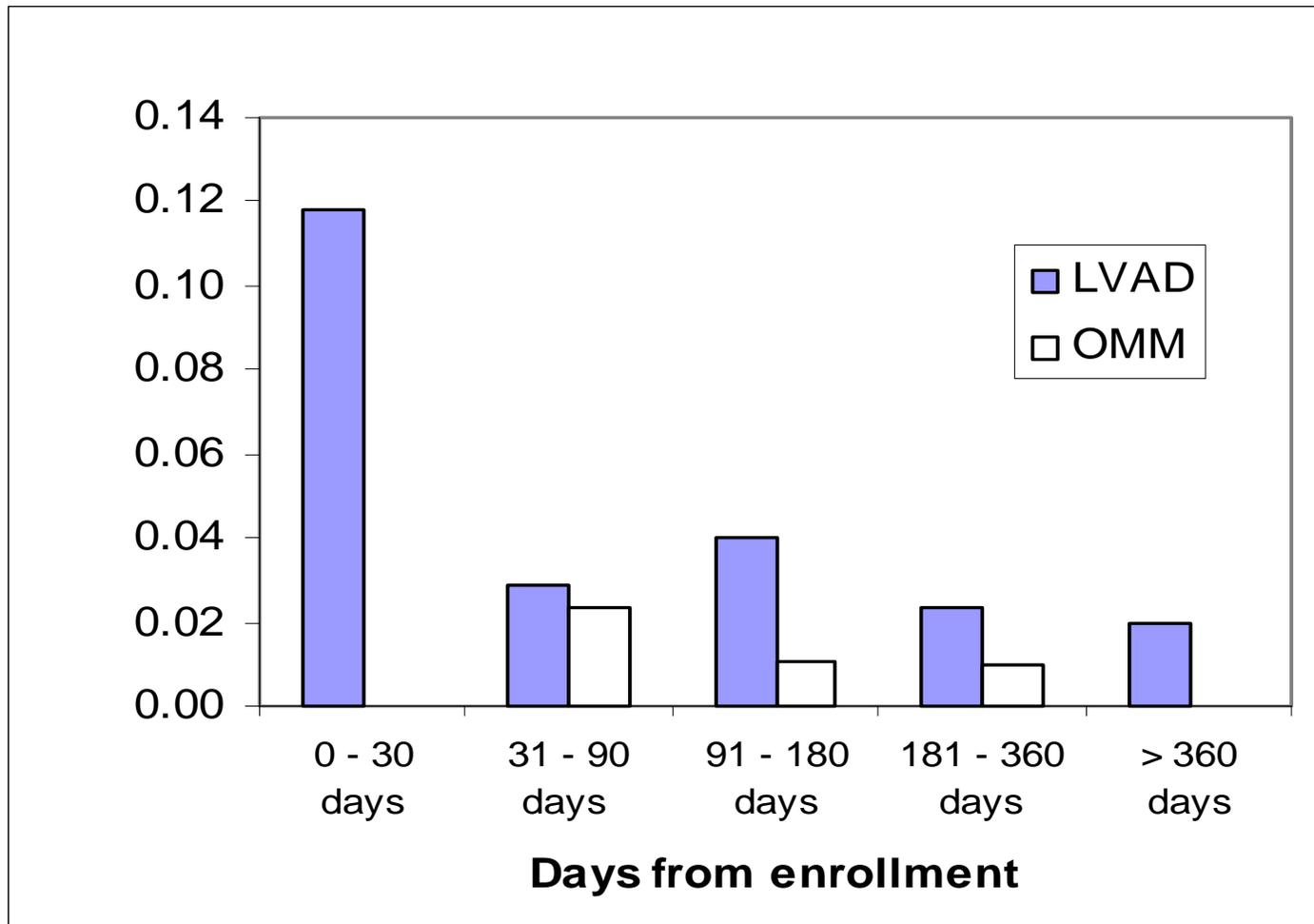
All-cause mortality reduced by 46%
in LVAD patients

Primary Objective of 33% Exceeded

Serious Adverse Events / 30 Pt days



Serious Neurologic Events /30 Pt days



Neurological Events in the LVAD Arm

LVAD Patients = 67

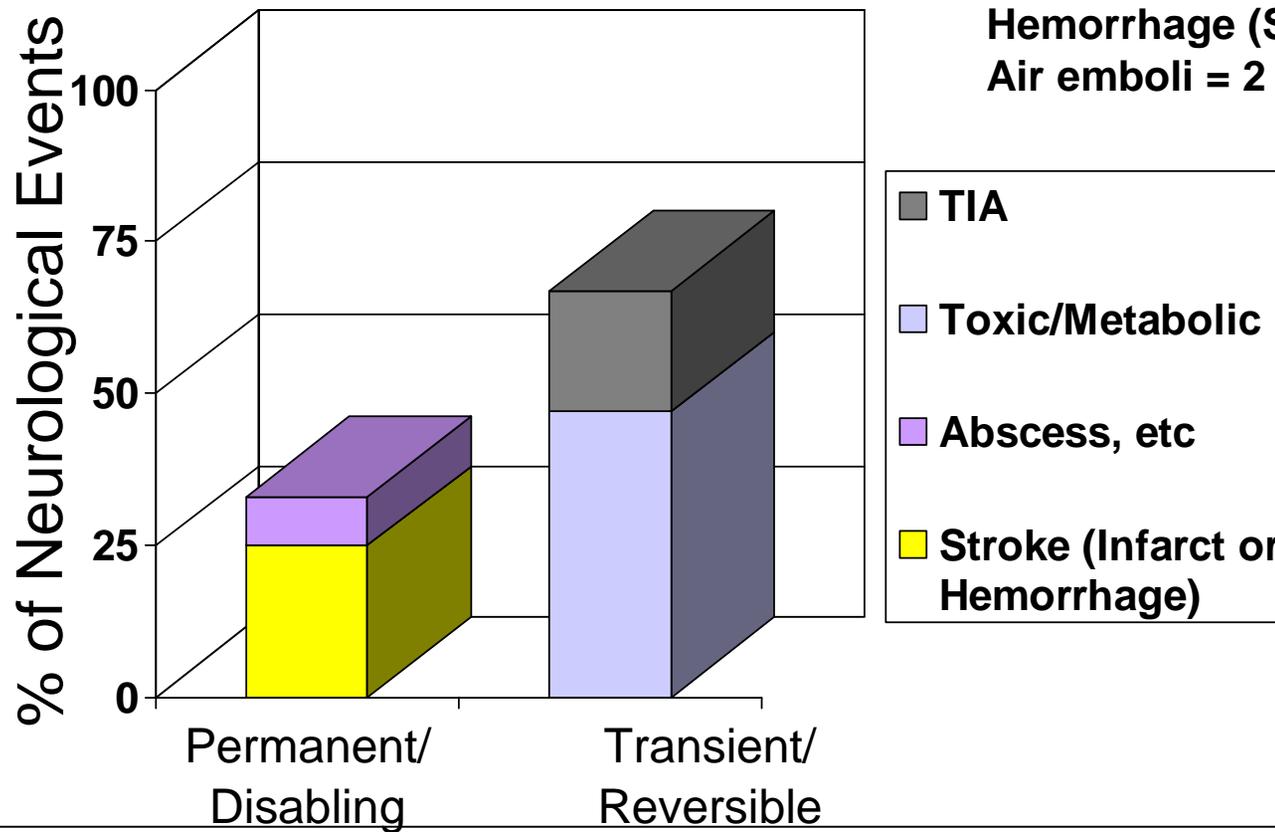
Neurological Events = 40

Stroke Subtype: N = 10

Ischemic = 6

Hemorrhage (SAH/ICH) = 2

Air emboli = 2



Bleeding & Infection Events

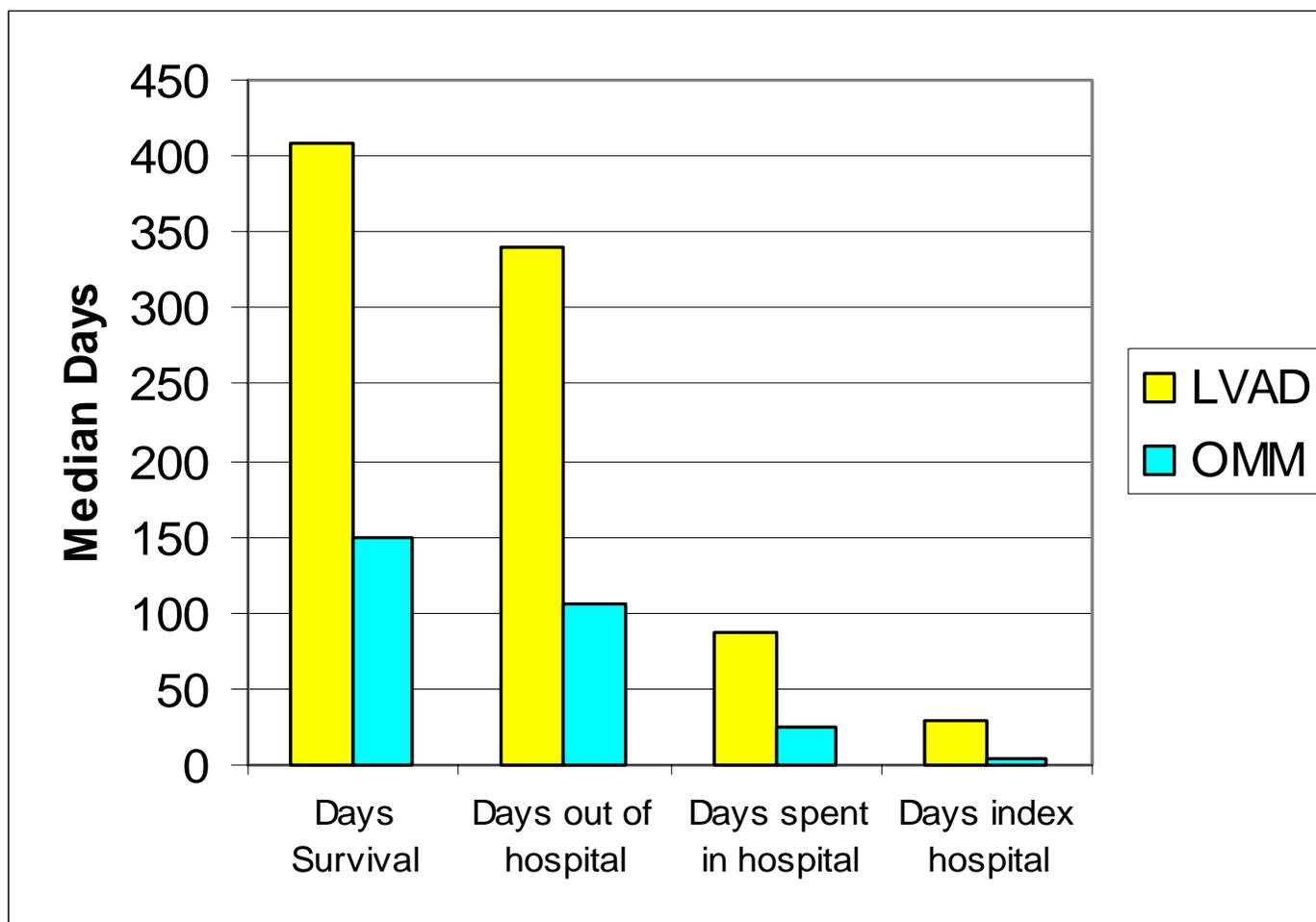
Bleeding:

- Majority of bleeds (67%) associated with LVAD implant or reimplant
- Similar to bridge experience

Infection:

- Specific complication of VAD use
- Initially unappreciated association with malnutrition
- Infection Guidelines developed

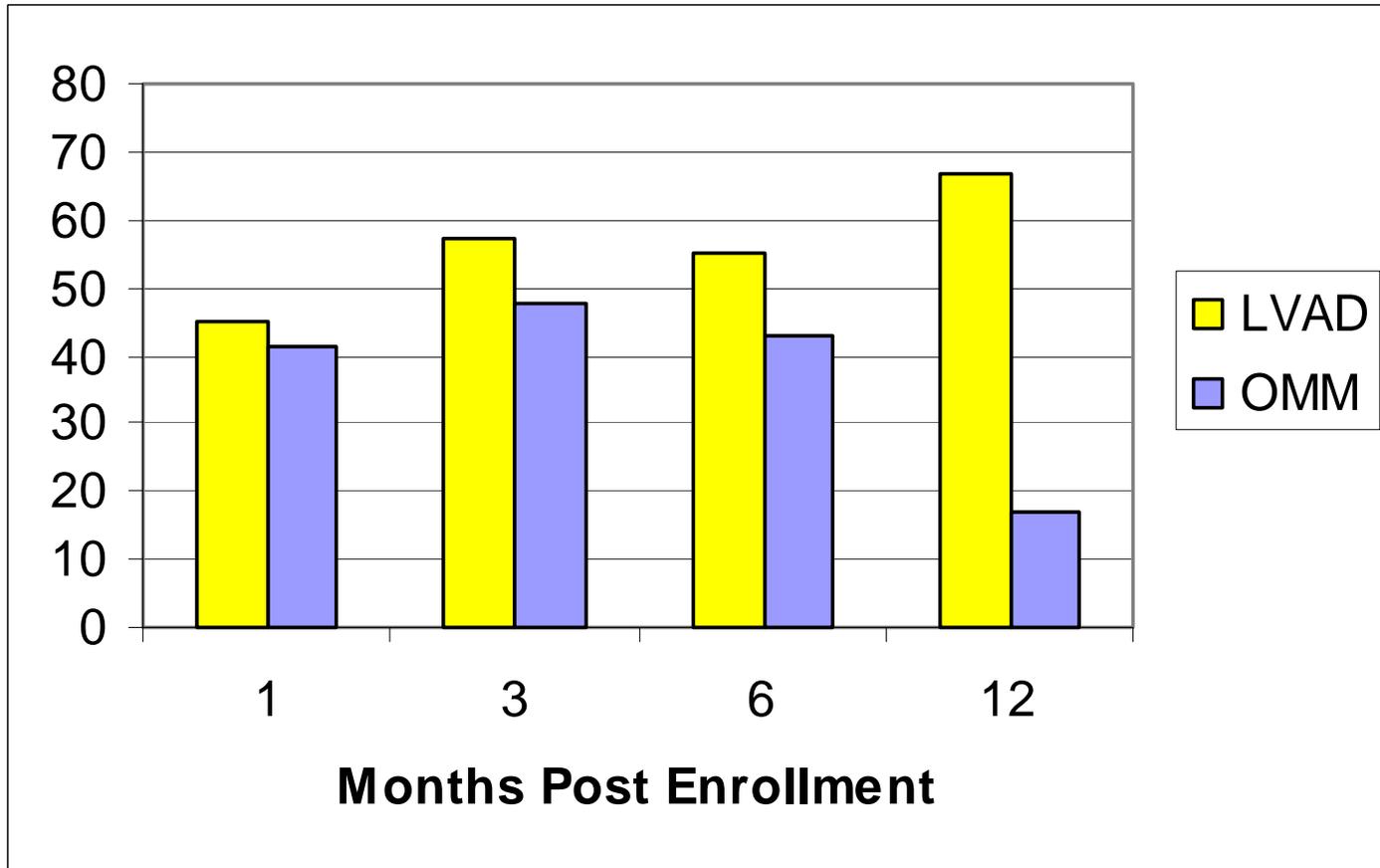
Median time spent in and out of hospital



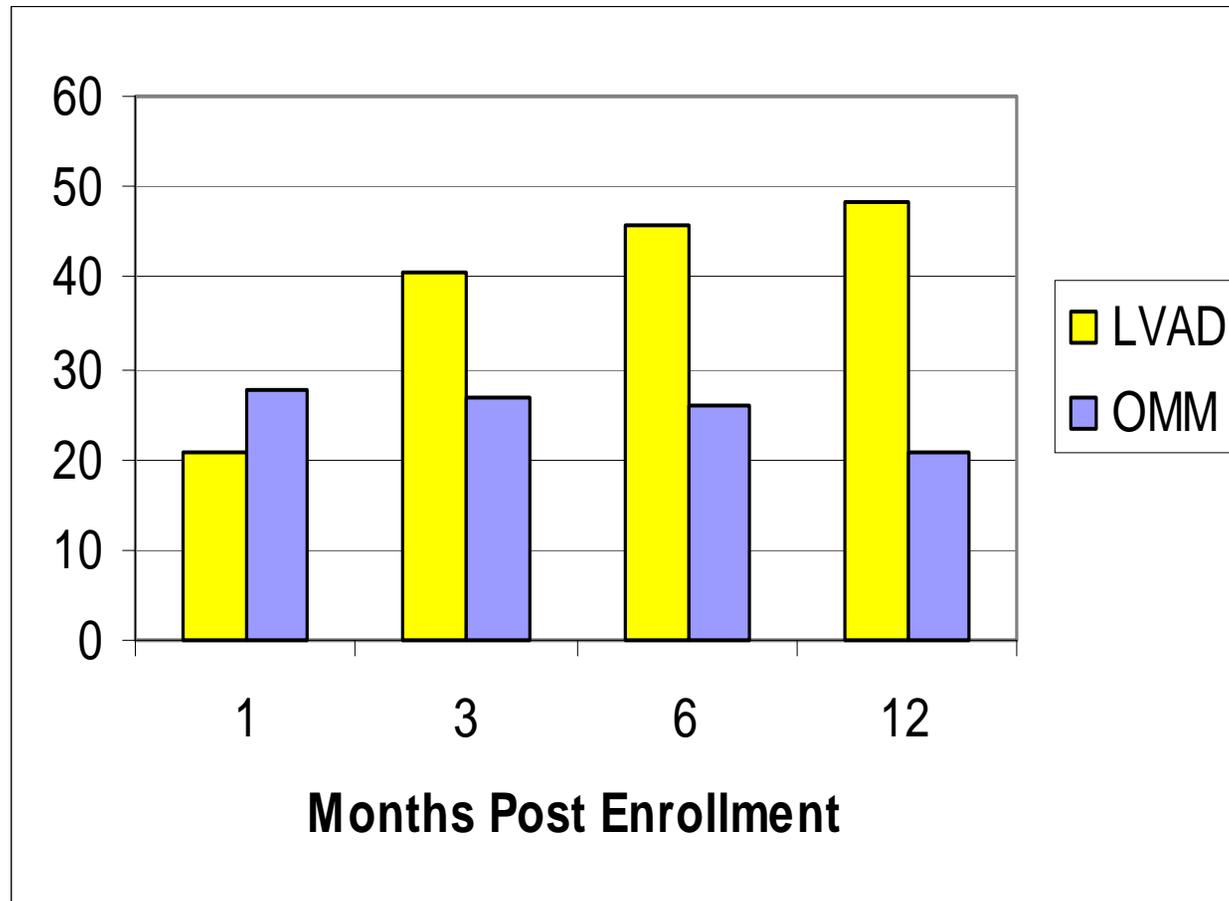
Quality of Life Assessment

- Hypothesis: QoL with LVAD should equal or exceed OMM group
- Instruments used:
 - SF-36 Health Survey (general health measure, 2 prespecified domains)
 - Minnesota Living with Heart Failure (disease specific QoL)
 - NYHA (functional status)
 - Beck Depression Inventory
 - EuroQOL (patient preferences)
- No QoL values imputed for dead patients

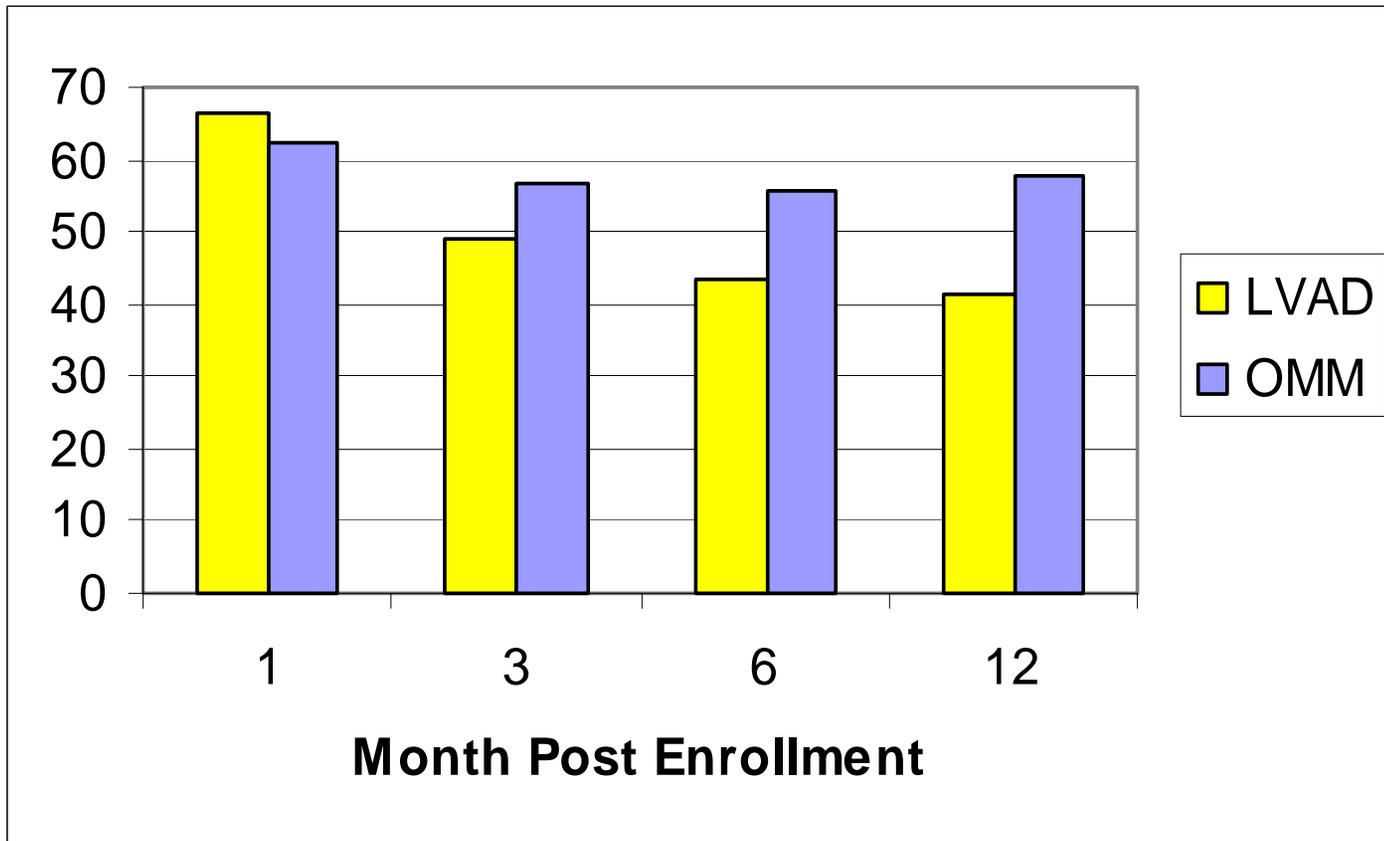
SF-36 Role/Emotional



SF-36 Physical Functioning

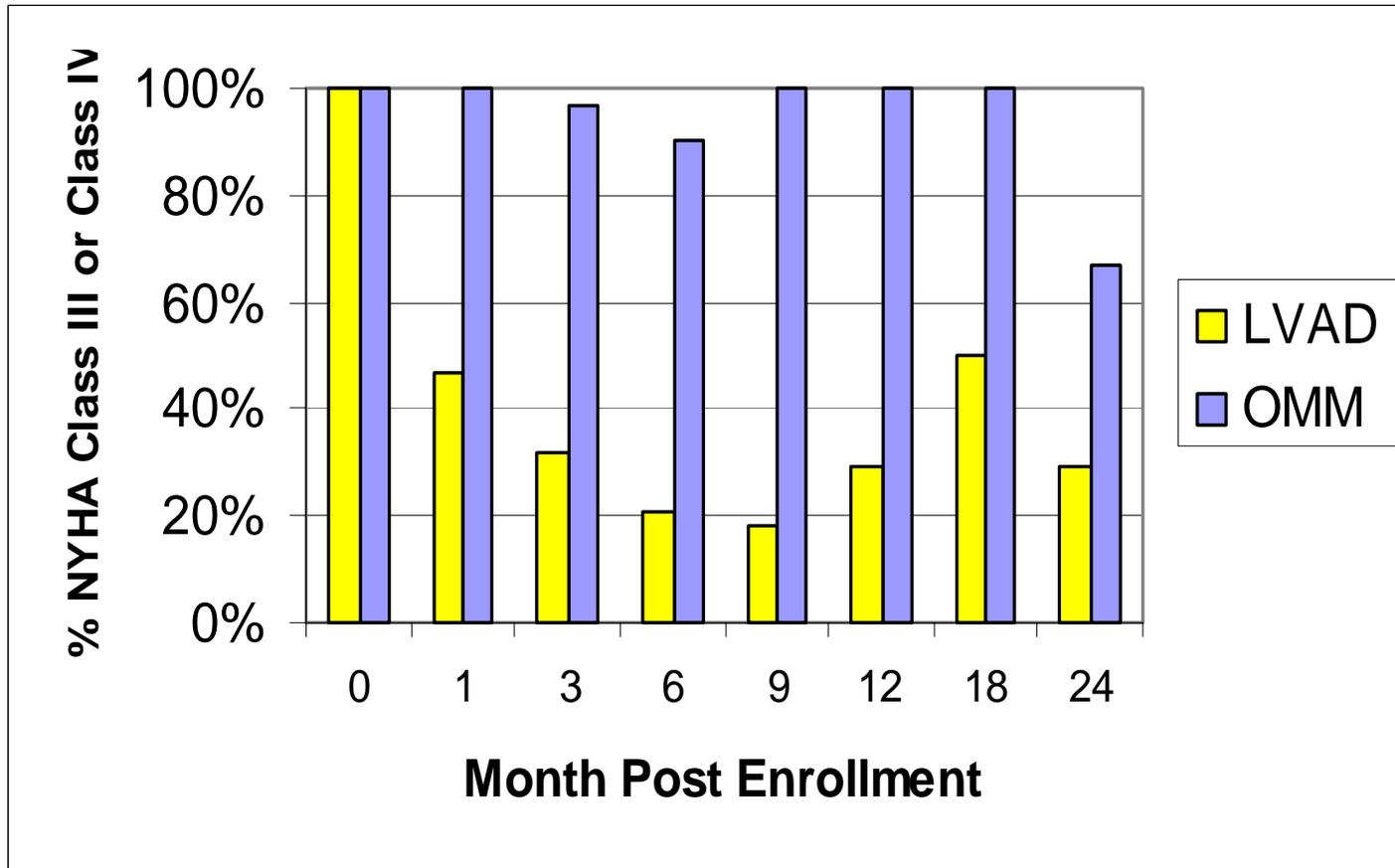


Minnesota Living with Heart Failure Total Score

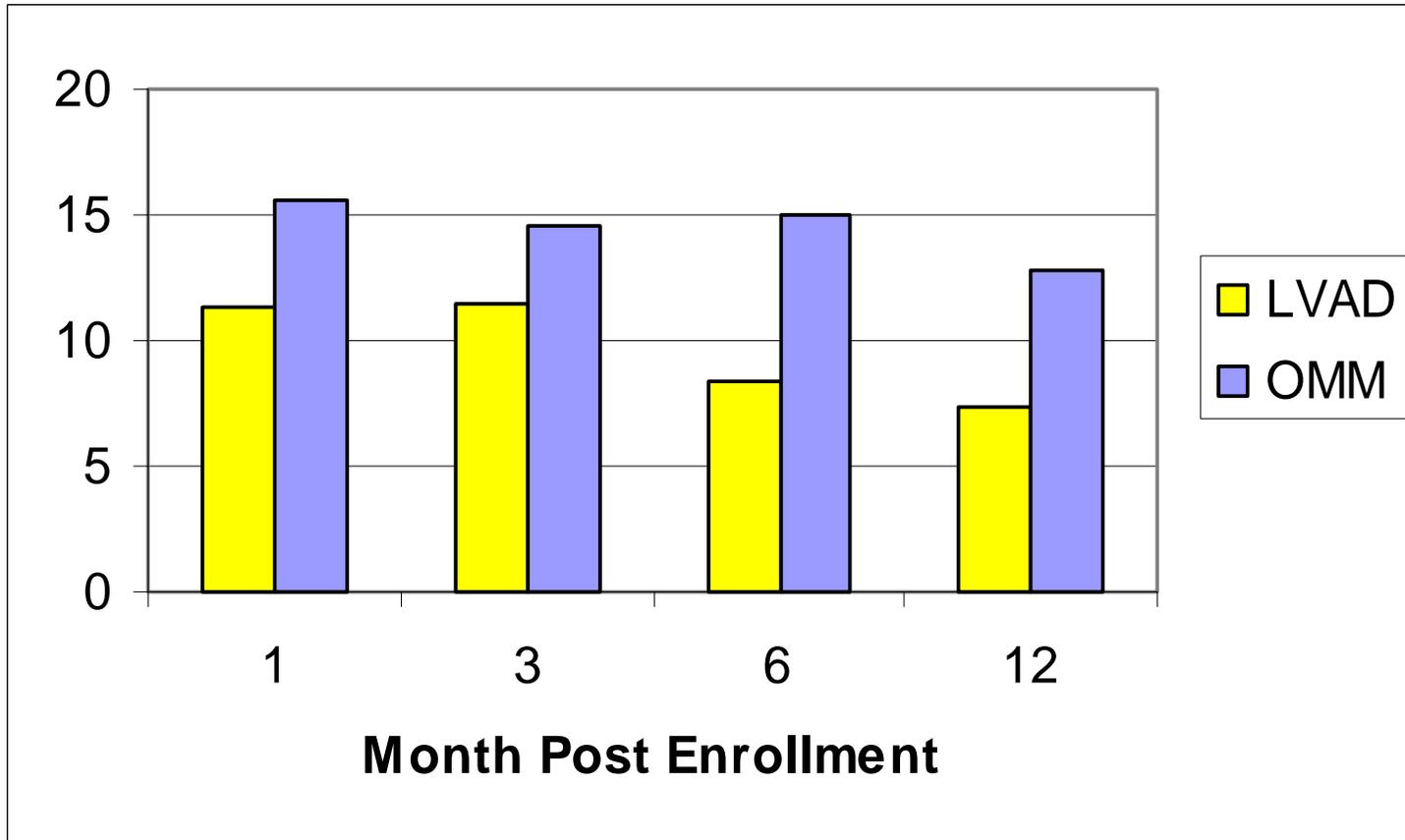


Lower score equals less effect of HF on daily activities

VE LVAS Improves NYHA Functional Class



Beck Depression Inventory



Clinical depression. 17

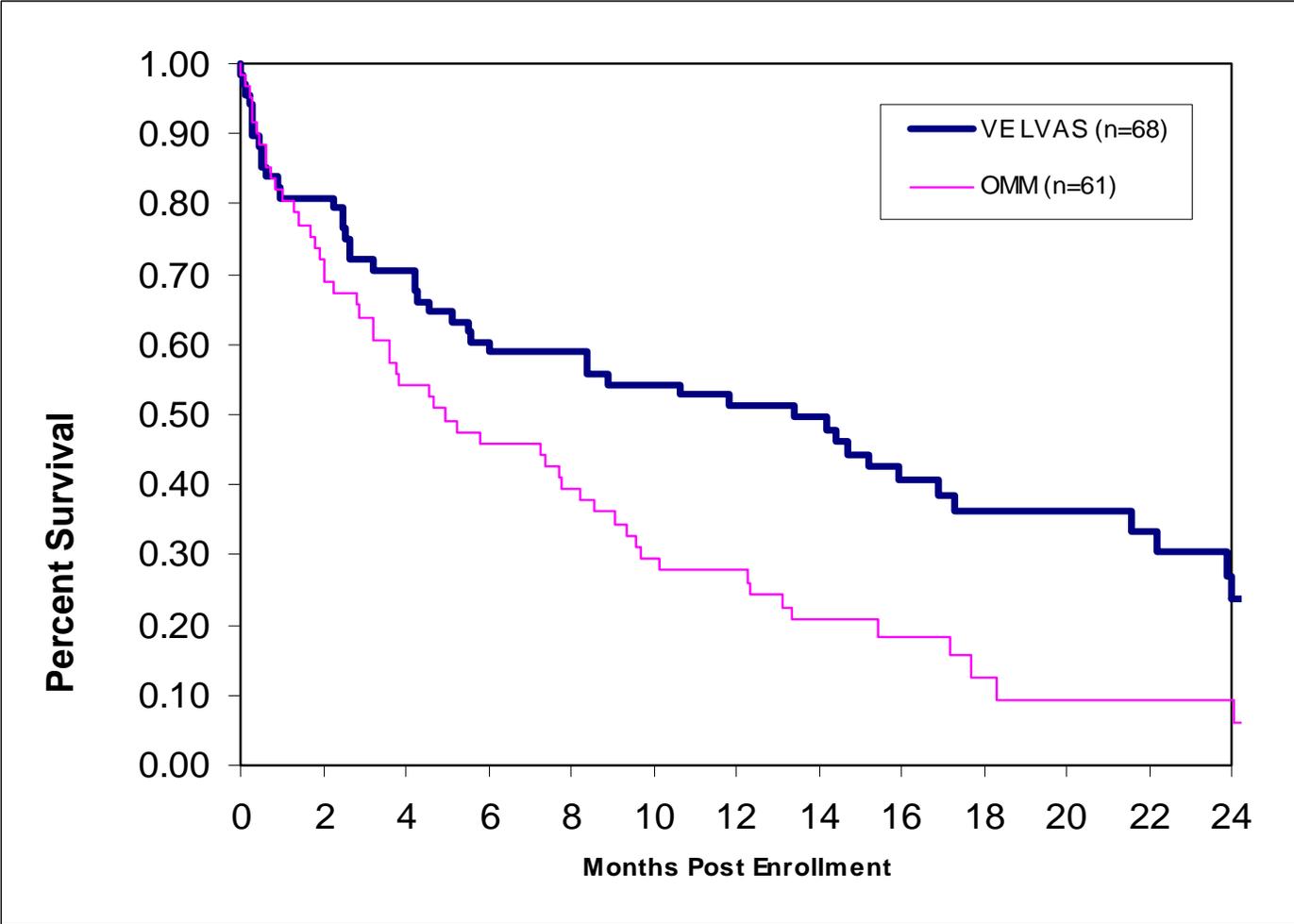
Summary of QoL Findings

- LVAD scores never worse than OMM (except short-term post-operative pain)
- LVAD generic QoL better than OMM at 12 months (key, pre-specified SF-36 domains)
- LVAD disease-specific QoL (MLHF) improved over OMM at 12 months but not significant statistically
- LVAD functional status (NYHA) significantly better than OMM
- LVAD reduced depressive symptoms to normal range (not seen in OMM)

QoL in Context

- LVAD physical function scores not normal, but analogous to patients receiving long-term hemodialysis and ambulatory heart failure patients
- LVAD emotional-role scores better than those reported for clinical depression and similar to those for ambulatory heart failure patients

Kaplan-Meier plot illustrating the probability of survival of LVAS versus OMM patients Feb 2002. Logrank analysis: $P=0.001$



Key Objective Conclusions

Efficacy

- Exceeded primary objective of trial by demonstrating that VE LVAS reduces all cause mortality in end-stage heart failure patients who are not candidates for cardiac transplantation
- Demonstrated statistical significance at 1 and 2 years.

Safety

- Incidence of AEs associated with implantation is higher than OMM patients
- Incidence of overall adverse events acceptable when compared to natural history of terminal illness
- Multiple opportunities for improvement identified

What is Meaningful Benefit?

Study (therapy)	1 year Mortality (%) Control vs Tx	1 yr Relative Benefit (%)	Absolute Benefit (%)
SOLVD (ACE Inhibitor)	14 vs 11	21	3
CONSENSUS (ACE Inhibitor)	62 vs 45	27	17
ATLAS (ACEI dosing)	14 vs 13.3	5	0.7
COPERNICUS (Beta Blocker)	18.5 vs 11	41	7.5
RALES (Spironolactone)	25 vs 17	32	8
REMATCH (LVAD)	76 vs 49	36	27



SUMMARY AND CLOSING REMARKS

Donald A. Middlebrook
Vice President, Regulatory Affairs and Quality
Assurance
Thoratec Corporation

Conclusions

Study scientifically validates safety and effectiveness:

- Strong evidence for clinically meaningful survival benefit
- VE LVAS is a well characterized, proven technology
- Reasonable evidence for safety particularly in context of terminal illness
- All QOL instruments showed sustained improvement trends over OMM
- Device provided unprecedented reduction in mortality in ESHF patients when compared to landmark drug studies
- VE LVAS is the only now proven alternative therapy for non-transplantable ESHF patients

**The HeartMate VE LVAS should
be approved for end stage
heart failure patients ineligible
for cardiac transplantation.**